# The Pharmacology of the Digitalis Drugs

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A summary of the actions of these drugs involves a survey of well-established conclusions and a critical examination of contrary opinions. Although experiments which appear to give opposite results are often in fact not comparable because of differences in technique, contradictions sometimes occur when such differences are not apparent; and, in that case, reference to individual papers is hardly possible without reference to all. Completeness of outline is thus prevented by the futility of trying, with limited space, to give a fair presentation of evidence in controversial matters.

## Sources and Nature.

Many plants of different natural orders contain poisonous principles with a similar characteristic action on the heart, and some of them have been used by uncivilized races as arrow-poisons, or for trial by ordeal. The active substances in such plants are nearly all chemically related glucosides, several of which are often found in the same plant. These drugs form the digitalis group, though only a few of them have yet obtained a firm foothold in medicine. A number of animal products also have a digitalis-like effect, but are not of therapeutic importance; while calcium and barium have actions on the heart which resemble in some respects the action of digitalis.

Great difficulty has been experienced in separating and purifying the various glucosides, but some have now been isolated and others at least identified as definite substances. The chief glucosides of therapeutic interest are included in the following list :—

| *Digitalis purpurea.* | *Digitalis lanata* | *Strophanthus* | *Squill* |
|---|---|---|---|
| Digitoxin, Gitalin, Gitoxin (from the leaves) | Digoxin | k-Strophanthin | Scillaren A |
| Digitalin (from the seeds) | Digilanid A | g-Strophanthin | Scillaren B |
| | Digilanid B | | |
| | Digilanid C | | |
| | Gitoxin | | |

The actions of these substances resemble each other closely. They differ in quantitative and time relations, but not in essential character. The glucosides are extremely poisonous. Their unusual toxicity would be much more apparent if they could reach the heart without loss. Digitoxin appears to be the most active of the D. purpurea group (Nativelle's digitalin is probably digitoxin), and the lanata glucosides are perhaps rather more powerful. The glucosides of squill (especially scillaren B) are more powerful than those of digitalis, and the strophanthus group have, in general, about the same activity as those of squill.

The lethal dose of these glucosides is much greater when given orally than when given by intravenous injection. Part of the drug is destroyed in the alimentary canal—probably more in the stomach than in the intestine—and part may be fixed by the liver, although this is somewhat doubtful. But loss of activity is due chiefly to slowness of absorption, typical of the group, which is in striking contrast to the rapid absorption of alkaloids. Strophanthin is absorbed even more slowly than digitoxin, and this explains the uncertainty of its action when preparations containing it are taken by mouth.

Pardee[8] found that when digitalis tincture was given in a dose of one minim per pound body-weight, the earliest electro-cardiographic sign of an action appeared in two to four hours. The maximum effect was reached in six to seven hours, and seemed to be maintained for twenty-four hours.

When the glucosides are injected they disappear quickly from the blood, not because they are destroyed, but probably because they are taken up by the tissues. The quantitative distribution in various tissues has not been finally established. The heart seems to have the greatest retaining power, the abdominal organs less, and the lungs none. The skeletal muscles are much inferior in this respect to the abdominal organs, but low specific fixation is more than compensated by their preponderance in the body. Weese[11] thinks that the glucosides may pass but once through the coronary circulation, because the blood may be cleared of them before it can return, and may contain, therefore, only freshly absorbed glucoside. This is not true when toxic amounts are given, and probably not even for therapeutic dosage, but it may be near enough the truth to indicate how small a proportion of the total dose has a chance of affecting the heart. And, in any case, only about ten per cent. of the whole circulation goes through the coronary arteries, so that much of the drug can be fixed by the tissues without reaching the heart-muscle at all.

The glucosides are slowly destroyed in the body, though there seems to be no direct evidence that any organ is specially concerned with their destruction. Traces are excreted by the intestine and kidneys, but excretion plays a subordinate part in their removal. A relatively large amount may reach the intestine in the bile, but, if so, the greater part of this is reabsorbed.

The duration of the effect of a single dose, and the possibility of accumulation when doses are repeated, will depend on the balance between rate of removal from the body and rate of absorption, and, in particular, on the tenacity with which the drug is retained by the heart-muscle. The digitalis glucosides accumulate more than those of strophanthus or squill, and the lanata glucosides do not seem very different in this respect from digitoxin. But evidence favouring accumulation is derived chiefly from determinations of the percentage of the lethal dose still needed to cause the death of animals which have already, some days previously, been given a known percentage of the lethal dose; and recent observations suggest that this may be evidence of accumulation of injury and not of the glucosides. Thus, three days after a toxic dose, areas of necrosis may appear in the heart-muscle, due, perhaps, to a disturbance of the coronary circulation. The strength of the heart may be increased on the first or second day after digitalis has been given, but later there may be observed a progressive decline in the functional condition, which corresponds to the onset of morphological changes.[1, 2, 12] In therapeutics, however, accumulation of effect is more likely to depend on accumulation of the drug, and deductions from the pathological results of toxic dosage must be made with caution.

Clinical experience has shown that the heart is more sensitive to digitalis in disease than in health. Even when compensation has been established, increased sensitivity remains. And this is confirmed by animal experiments in which cardiac insufficiency has been produced.

No drug removes completely the effects of digitalis, though a few are partial antagonists (quinine, quinidine, etc.). Sympathomimetic drugs may increase the tendency to fibrillation. Stewart and Rogoff[9] found that irregularities caused by strophanthin disappeared when the outflow of suprarenal secretion was prevented, and appeared again when adrenaline entered the circulation.

There is no clear experimental evidence that digitalis protects the heart against either anæsthetics or bacterial toxins.

## Action.

*Rate.*—The reduction of heart-rate with moderate doses of digitalis is prevented in mammals by section of the vagi, or by atropine. Action through the vagus has been attributed by Cushny[3] to direct stimulation of the vagal centre; by Straub[10] to an increase in the sensitivity of the heart to unaltered vagal impulses; by Hering,[5] Heymans,[6] and their co-workers tc reflex vagal stimulation initiated in the carotid sinus by a rise of blood-pressure. The reflex theory is well supported by experimental work; and although in man a rise of blood-pressure is not observed with therapeutic dosage, it may in fact be abolished by the reflex which it causes. Only a small stimulus is needed, for the slowing of the pacemaker is not great, and the heart may be more sensitive to vagal stimuli, as Straub believes. The treatment of auricular fibrillation with digitalis results in a greater decrease of pulse-rate, which has, however, a different origin.

*Tone and Contractility.*—Moderate doses of the glucosides cause apparently an increase of tone and strength of contraction but, in health, no increase in the output of blood from the heart. The size of the heart-shadow is thus reduced and the displacement of the cardiac border more evident, while a fall in the circulation-rate often occurs. In cardiac disease the heart-shadow shows similar changes under digitalis, but these are more definite because dilatation is relieved. Either an increase or a decrease in circulation-rate may be observed, the result depending, perhaps, on the degree of cardiac failure that existed. More powerful contractions need not augment the output of blood, because, if the tone is greater, diastolic filling may be less complete; while extracardiac factors influence the return of blood to the heart, and thus the amount that contraction can expel. And of some importance, also, is the observation that both in health and in cardiac disease, digitalis can lessen the actual quantity of circulating blood, probably by increasing storage in various reservoirs.

Wollheim[13] describes two types of decompensation. In one type (associated with hypertonus, aortic insufficiency, etc.) the amount of blood in the circulation is increased, and the effect of digitalis is beneficial. In the other, usually cyanotic, type (associated with pulmonary or mitral stenosis and other conditions) the circulating blood is reduced, and digitalis has an unfavourable effect.

The powerful contractions, however, enable the heart to empty itself more completely, so that, without changes in rate, venous flow, and arterial resistance, the same amount of blood may be expelled from a smaller cardiac volume.

Contraction is more rapid and the emptying time is shorter when therapeutic doses of digitalis have been given. The maximum intraventricular pressure is probably higher.

The increase in tone and in power of contraction is the result of a direct action of the glucosides on the muscle of the heart, and is not prevented by atropine or by vagal section. According to Cushny,[4] the normal heart often relaxes more completely under digitalis, but this is due to stimulation of the vagus and is not observed after atropine. Since the heart would thus contain more blood, the output per beat would be greater, even if the power of contraction were unaltered; a conclusion apparently not in harmony with more recent observations of the effects of therapeutic dosage in normal man. In any case, there seems to be general agreement that when the heart is dilated, the direct action of digitalis renders diastole less complete and so reduces the dilatation.

*Conduction.*—Conduction of impulses from the auricle to the ventricle is depressed by stimulation of the vagus. In mammals, if the heart is normal, digitalis acts on conduction through the vagus, and its effect is therefore removed by atropine, while very large amounts of the drug are needed for a direct action on the conducting fibres. In disease of the heart, however, and in certain experimental conditions, the glucosides appear to act directly on conduction, and atropine does not prevent the effect of therapeutic doses.

No other action of digitalis has so great importance in treatment. When auricular fibrillation occurs, very numerous and irregular impulses are generated in the auricle, and these cause frequent and irregular contractions of the ventricle. The filling time between the contractions is too short, and partial failure of the circulation results. If the conducting mechanism is depressed by digitalis, many auricular impulses never reach the ventricle, and a slower and more regular ventricular rhythm is established; while fibrillation of the auricle continues but does not involve circulatory failure.

In auricular flutter a similar partial block may be produced by digitalis, and the pulse become less frequent while the auricular rate is maintained. But often, under digitalis, the flutter passes into fibrillation, and if treatment is then stopped the auricle may resume its normal rhythm.

*Irregularities caused by digitalis.*—Sinus irregularities sometimes occur and affect the whole cardiac rhythm. They are due to an action through the vagus, and are removed by atropine.

The tendency to spontaneous contraction is increased, and extrasystolas may originate in any part of the cardiac muscle—more commonly, however, in the ventricle than in the auricle. One of the most frequent irregularities is bigeminal rhythm, in which each normal beat seems to arouse an autogenous beat, so that extrasystoles alternate with normal contractions. Very rarely auricular fibrillation has appeared in patients who had previously a regular rhythm.

Pulsus alternans is also a rare occurrence in treatment with digitalis. In animal experiments a similar condition is observed occasionally as an antecedent to partial block, but its significance is uncertain.

Depression of conductivity in the A-V bundle, though valuable in auricular fibrillation, may be objectionable in other disorders. Partial block is often at first of inhibitory origin, and can be relieved by atropine; but with higher dosage of digitalis a direct action on the conducting fibres may supervene.

*Effect on the electro-cardiogram.*—There is apparently no fixed relation between dosage and electro-cardiographic changes; great quantitative differences are observed, not only with different glucosides, but also in different individuals, although qualitatively the effects are similar. Whether these changes are the expression of a toxic or a therapeutic action seems doubtful. In some clinical investigations the P-R interval has been longer and the T-wave flattened or inverted, while other observations have revealed partial A-V block but no typical change in the T-wave. And in the normal human heart the T-wave may show no characteristic change, even with toxic dosage. The importance of vagal action cannot be denied, though Lagen and Sampson[7] have found that the electro-cardiogram of the chick embryo heart is affected in much the same way by digitalis, whether tested before or after the ingrowth of nerve-fibres.

*Effects of toxic dosage on the mammalian heart.*—Early results of toxic doses correspond to the therapeutic effects in man. The rate is reduced unless inhibitory impulses are prevented from reaching the heart; while the contractions are stronger, whether the vagi are cut or intact. Sometimes, at a later stage, inhibitory slowing becomes extreme, so that, even if each powerful systole expels more blood, the total output is not maintained. Conduction begins to fail and heart-block appears, at first partial, then complete, with separate auricular and ventricular rhythms. The spontaneity of the cardiac muscle is greatly exaggerated, and inhibitory control is lost. Extrasystoles may arise from any point in the heart, and the beats become more and more frequent and irregular, until the ventricle fibrillates and blood is no longer expelled.

*Vomiting.*—Vomiting is a clinical sign of overdosage with digitalis. Its occurrence is earlier with intravenous than with oral administration, and this has led to the belief that it is induced by a central action. But, in contrast to apomorphine, the glucosides have no emetic effect when applied directly to the vomiting centre. These observations suggest that the stimulus is initiated at some peripheral point outside the stomach; and an action on the heart cannot be excluded as a possible cause of the reflex.

*Diuresis*.—In animal experiments often no diuresis is observed; but when water has been given previously, the glucosides may hasten its excretion and augment the output of chloride. Even when diuresis occurs, the renal blood-flow is seldom increased, though the oxygen consumption of the kidneys is greater.

Diuresis in cardiac œdema is attributed by Cushny[4] to the action on the heart. Because the circulation in all parts of the body is improved, fluid leaves the tissues to enter the capillaries, and the kidneys respond as usual to dilution of the blood. Cushny's view does not seem inconsistent with a decrease in the circulation-rate sometimes observed in recent experiments. For the essential result of successful treatment with digitalis is improvement in the circulation, however this may be revealed; and the advantage may well be derived from a fall in venous and capillary pressure, so that fluid can be drawn more readily from the tissues by the osmotic tension of the plasma colloids.

Against the cardiac origin of diuresis is clinical experience of differences in the diuretic effects of various glucosides, without corresponding differences in their effects on the heart. But, while other actions may be admitted as possible subsidiary factors, the relief of cardiac œdema must depend ultimately on the degree to which a normal circulation can be approached, and therefore on the success with which the function of the heart can be restored.

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